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Non-compartmental pharmacokinetics analyses (NCA) were postdose, and were assayed for moxifloxacin. QTc prolongation (∆∆QTc). Blood samples were collected from all at least 90 minutes prior to dosing through 20 hours postdose. QT serial blood collections and once for collection of electrocardiogram group at dose levels of 0 (control), 10, 50 and 175 mg/kg, once for Moxifloxacin was administered orally twice to nine male monkeys/dogs) with methodologies such as jacketed external telemetry with blood pressure measurement (JET-BP).

The purpose of this study was to characterize the population pharmacokinetics and pharmacodynamics of moxifloxacin after oral administration to male cynomolgus monkeys with ECG data collected using JET-BP, and evaluate the suitability of JET-BP for detection of drug-treatment induced QTc interval prolongation.

Methods
Moxifloxacin was administered orally twice to nine male monkeys’ group at dose levels of 0 (control), 10, 50 and 175 mg/kg, once for serial blood collections and once for collection of electrocardiogram (ECG) data. Continuous ECG data were collected using JET-BP for at least 90 minutes prior to dosing through 20 hours postdose. QT intervals were corrected by heart rate (QTc interval), control group animal, and time zero values from individual animals to obtain net QTc prolongation (ΔQTc). Blood samples were collected from all animals predose and approximately 0.5, 1, 2, 3, 4, 8 and 24 hours postdose, and were assayed for moxifloxacin.

Non-compartmental pharmacokinetics analyses (NCA) were performed using Phoenix® WinNonlin® (Certara USA, Inc., Princeton, NJ). Population Pharmacokinetic/Pharmacodynamic (PopPKPD) analyses were performed using Phoenix NLME® (Certara USA, Inc., Princeton, NJ). A one compartment model was selected for the pharmacokinetic structure model, and a linear proportional model was used for the PD model based on literature and data diagnosis with QTc prolongation being proportional to moxifloxacin concentration. A sequential PK/PD modeling strategy was used, with the PK data predicted from the previously developed population PK model.

Body weight was evaluated as covariate for effects on the model and was found to have no effects on both moxifloxacin pharmacokinetic and QTc prolongation (data not presented).

Prolongation in Male Cynomolgus Monkeys with ECG Data Collected Using JET-BP

Figure 1. Mean (±SD) concentrations (ng/mL) of moxifloxacin in male monkey plasma.

A linear proportional model was selected for the relationship between ΔQTc and moxifloxacin concentrations expressed as $\Delta QTc = \alpha + \beta C$, where $\alpha$ is a constant, $\beta$ is the slope of the linear relationship.

The results (Figure 6 and Table 3) indicated that with an increase in moxifloxacin concentration of 1 ng/mL, there would be a mean QTc interval prolongation of 0.0036 ms (3.6 ms/(µg/mL), or 1.44 ms/µM), which was similar to literature reported value of 1.5 ms/µM.

Conclusions
The PopPKPD modeling showed that the effect of moxifloxacin on QTc interval prolongation in monkeys was well described using a direct linear model. The relationship between moxifloxacin exposure and QTc interval prolongation was similar to literature values, indicating the JET-BP is suitable for evaluation of drug-treatment induced QTc interval prolongation.

Reference